COMMENT
Gastroenterology & Hepatology Research 2023;5(4):20. https://doi.org/10.53388/ghr2023-03-084

Repairing mitochondrial dysfunction: potential mechanisms of natural products in the treatment of NAFLD

Si Wang[1#], Li-Wei Xing[1#], Jia-Bao Liao[1#], Huan-Tian Cui[1], Wei-Bo Wen[1*], Ning Wang[1*]

[1]The First School of Clinical Medicine, Yunnan University of Chinese Medicine, Kunming 650500, China.

[#]Si Wang, Li-Wei Xing and Jia-Bao Liao are the co-first authors of this paper.

[*]**Corresponding to:** Wei-Bo Wen. Ning Wang. The First School of Clinical Medicine, Yunnan University of Chinese Medicine, Kunming 650500, China. E-mail: wenweibo2020@163.com, wnworkemail@163.com.

Non-alcoholic fatty liver disease (NAFLD), also known as MAFLD, is a chronic liver disease characterized by dyslipidemia and excessive steatosis in hepatocytes [1]. With the acceleration of urbanization, the problems of physical activity reduction and nutritional imbalance are becoming increasingly prominent. The prevalence of NAFLD has reached 25% globally [2], and it is also showing a trend of continuous growth and younger onset ag[3]. Although numerous studies have confirmed that the pathogenesis of NAFLD may be related to genetic susceptibility, gene polymorphism, intestinal microenvironment disorder, insulin resistance, and other factors [4], the "two-hit" theory also reveals the mechanism of the occurrence of some NAFLD, there is still a lack of effective and stable drugs that can inhibit the progression of NAFLD to liver fibrosis and even liver cancer in the treatment of NAFLD [5], which poses a serious threat to human health and imposes a heavy burden on the socio-economy [6]. It is particularly important to further explore the etiology and pathogenesis of NAFLD, providing ideas and directions for the development of new drugs against NAFLD [7].

Mitochondria are double-membrane organelles with multiple important biological functions and interconnections within cells, including mtDNA, which encodes 13 proteins and auxiliary RNAs related to mitochondrial oxidative phosphorylation in the mitochondrial matrix [8]. They participate in the biosynthesis of nucleotides, fatty acids, cholesterol, amino acids, and heme, and have functions such as regulating lipid metabolism, oxidative phosphorylation, and oxidative stress [9]. They play an important role in maintaining the dynamic balance between fat oxidation and ROS production in the liver, promoting stress responses such as autophagy to protect hepatocytes [10]. Mitochondria are crucial for the normal functioning of the liver, including a series of processes ranging from substrate metabolism and energy production to cell signaling, and then to the biotransformation of exogenous substances [11]. Accumulated recent studies revealed the importance of mitochondrial dysfunction during the progression of NAFLD. A recent review published in "Journal of Hepatology" by Bernard Fromenty et al. summarized the role of mitochondrial dysfunction in NAFLD pathogenesis. Excessive fatty acid could contribute to the dysfunction of hepatic mitochondria, characterized by abnormal morphological changes, reduced respiratory chain activity, ATP depletion, increased outer and inner membrane permeability, excessive ROS production, oxidative stress-mediated double-stranded circular mitochondrial DNA (mtDNA) deletion, and mitochondrial β oxidation damage, these abnormal manifestations could further aggravate the dysfunction of lipid metabolism in liver. When mitochondria are dysfunctional, it will promote the excessive production of ROS, induce oxidative stress, damage liver cells, and further promote the occurrence of inflammatory reactions and oxidative stress [12]. Therefore, by directly or indirectly intervening to repair the dysfunction of liver mitochondria, it can have beneficial effects on the prevention and treatment of NAFLD. Rector RS et al. [13] also confirmed this point. The research results found that mitochondrial dysfunction occurred before NAFLD in the liver of obese OLETF (a spontaneous type 2 diabetes model) rats, indicating that progressive mitochondrial dysfunction may be an important link in promoting the natural course of NAFLD (Figure 1).

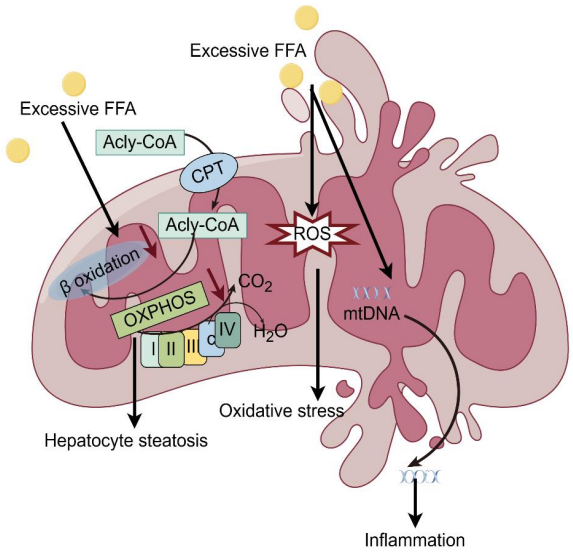

Figure1 The association between mitochondrial dysfunction and NAFLD. (By Figdraw.).

Natural products are an important source for the development of new drugs, including extracts from animals, plants, or components or metabolites from microorganisms. They have the characteristics of diverse structures and a wide range of sources. Studies have shown that natural polyphenols represented by curcuminl [14] and resveratro [15], natural flavonoids represented by nobiletin [16] and silymarin [17], natural alkaloids represented by tomatidine [18] and berberine [19], and natural polysaccharides represented by angelica polysaccharide and Lycium barbarum polysaccharide [20] can alleviate the occurrence and development of NAFLD by regulating lipid and cholesterol metabolism, insulin sensitivity, liver oxidative stress, and liver inflammation in NAFLD model mice/rats. However, it has also been pointed out that the results of clinical trials targeting the treatment of NAFLD with natural products are not completely consistent with the results of animal experiments. For example, Heebøll S et al. [21]found that resveratrol intervention in NAFLD patients not only failed to benefit patients by improving insulin resistance, and may also cause some adverse reactions such as fever and dual blood cell reduction. Therefore, it is important to explore new potential therapeutic targets and verify the safety and effectiveness of these natural products in clinical applications. This will provide new possibilities for the search for biomarkers and the treatment of NAFLD.

Hymavathi R et al. [22] conducted an experiment using green tea extract (polyphenols) to intervene in NAFLD rats. The experimental results showed that green tea polyphenols can repair the damage to mitochondrial DNA in rat hepatocytes by reducing ROS levels, reducing the frequency of D-loop mutations in mtDNA, and affecting mitochondrial replication, transcription, and/or biogenesis, thereby

affecting mitochondrial function as a whole. Zhu Y et al. [23] also found that after intervention with ginsenoside Rg5 in NAFLD mice, mitochondrial mass in hepatocytes significantly increased, and the Sirt1/PGC-1α/mitofusin-2 mitochondrial biosynthesis pathway was activated, leading to significant improvement in liver oxidative stress and inflammation in mice, thereby exerting therapeutic effects on NAFLD. Sirt3 is mainly located in mitochondria and has a key role in regulating mitochondrial energy metabolism by deacetylating and modifying multiple mitochondrial proteins. Zhang L et al. [24] found that resveratrol can upregulate Sirt3 expression, improve mitochondrial ATP synthase activity and basal respiratory rate, thereby reducing fatty acid oxidation and triglyceride accumulation, and reducing ROS expression, stopping the vicious cycle of "mitochondrial dysfunction-oxidative stress-mitochondrial damage" in NAFLD to protect the liver, without any adverse reactions. Therefore, it can be inferred that repairing mitochondrial dysfunction may be a potential effective mechanism for natural products to treat NAFLD.

In recent years, people have gradually realized that NAFLD may be a "mitochondrial disease", and the functional changes of liver mitochondria run through the occurrence and development of NAFLD, among which mitochondrial oxidative stress is a key factor in the progression of NAFLD. It will provide new ideas for the treatment of NAFLD and related metabolic diseases such as obesity, type 2 diabetes, cardiovascular disease to carry out in-depth research on promoting lipid peroxidation, inhibiting the generation of reactive oxygen species, maintaining mitochondrial homeostasis, protecting mitochondria, and develop natural products to target the intervention of NAFLD disease progress.

References

1. Cotter TG, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. *Gastroenterology* 2020;158(7):1851–64. Available at: http://doi.org/10.1053/j.gastro.2020.01.052
2. Younossi ZM. Non-alcoholic fatty liver disease – A global public health perspective. *J Hepatol* 2019;70(3):531–44. Available at: http://doi.org/10.1016/j.jhep.2018.10.033
3. Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism* 2020;111:154170. Available at: http://doi.org/10.1016/j.metabol.2020.154170
4. Liu QH, Zhao Y, Hu YY. The effect of diet on gut microbiota associated with non-alcoholic fatty liver disease. *J Clin Hepatol* 2021;37(04):939-942.
5. Elhence A, Shalimar. Treatment of non-alcoholic fatty liver disease-Current perspectives. *Indian J Gastroenterol* 2020;39(1):22–31. Available at: http://doi.org/10.1007/s12664-020-01021-2
6. Gheshlaghi L, Chegeni M, Nili S, et al. Prevalence of non-alcoholic fatty liver and its related factors in Iran: Systematic review and meta-analysis. *J Edu Health Promot* 2023;12(1):356. Available at: http://doi.org/10.4103/jehp.jehp_1056_22
7. Meng D, Zhang F, Yu W, et al. Biological Role and Related Natural Products of SIRT1 in Nonalcoholic Fatty Liver. *Diabetes Metab Syndr Obes* 2023;16:4043–64. Available at: http://doi.org/10.2147/DMSO.S437865
8. Calvo SE, Mootha VK. The Mitochondrial Proteome and Human Disease. *Annu Rev Genom Hum Genet* 2010;11(1):25–44. Available at: http://doi.org/10.1146/annurev-genom-082509-141720
9. Angajala A, Lim S, Phillips JB, et al. Diverse Roles of Mitochondria in Immune Responses: Novel Insights Into Immuno-Metabolism. *Front Immunol* 2018;9. Available at: http://doi.org/10.3389/fimmu.2018.01605
10. Vercellino I, Sazanov LA. The assembly, regulation and function of the mitochondrial respiratory chain. *Nat Rev Mol Cell Biol* 2021;23(2):141–61. Available at: http://doi.org/10.1038/s41580-021-00415-0
11. Ramanathan R, Ali AH, Ibdah JA. Mitochondrial Dysfunction Plays Central Role in Nonalcoholic Fatty Liver Disease. *Int J Mol Sci* 2022;23(13):7280. Available at: http://doi.org/10.3390/ijms23137280
12. Fromenty B, Roden M. Mitochondrial alterations in fatty liver diseases. *J Hepatol* 2023;78(2):415–29. Available at: http://doi.org/10.1016/j.jhep.2022.09.020
13. Rector RS, Thyfault JP, Uptergrove GM, et al. Mitochondrial dysfunction precedes insulin resistance and hepatic steatosis and contributes to the natural history of non-alcoholic fatty liver disease in an obese rodent model. *J Hepatol* 2010;52(5):727–36. Available at: http://doi.org/10.1016/j.jhep.2009.11.030
14. Lee DE, Lee SJ, Kim SJ, Lee H-S, Kwon O-S. Curcumin Ameliorates Nonalcoholic Fatty Liver Disease through Inhibition of O-GlcNAcylation. *Nutrients* 2019;11(11):2702. Available at: http://doi.org/10.3390/nu11112702
15. Andrade JMO, Paraíso AF, de Oliveira MVM, et al. Resveratrol attenuates hepatic steatosis in high-fat fed mice by decreasing lipogenesis and inflammation. *Nutrition* 2014;30(7–8):915–19. Available at: http://doi.org/10.1016/j.nut.2013.11.016
16. Peng Z, Li X, Xing D, et al. Nobiletin alleviates palmitic acid-induced NLRP3 inflammasome activation in a sirtuin 1-dependent manner in AML-12 cells. *Mol Med Rep* 2018; 18(6):5815-5822. Available at: http://doi.org/10.3892/mmr.2018.9615
17. Peng J, Li Q, Li K, et al. Quercetin Improves Glucose and Lipid Metabolism of Diabetic Rats: Involvement of Akt Signaling and SIRT1. *J Diabetes Res* 2017;2017:1–10. Available at: http://doi.org/10.1155/2017/3417306
18. Wu SJ, Huang WC, Yu MC, et al. Tomatidine ameliorates obesity-induced nonalcoholic fatty liver disease in mice. *J Nutr Biochem* 2021;91:108602. Available at: http://doi.org/10.1016/j.jnutbio.2021.108602
19. Shan M, Dai Y, Ren X, et al. Berberine mitigates nonalcoholic hepatic steatosis by downregulating SIRT1-FoxO1-SREBP2 pathway for cholesterol synthesis. *J Integr Med* 2021;19(6):545–54. Available at: http://doi.org/10.1016/j.joim.2021.09.003
20. Wang K, Cao P, Wang H, et al. Chronic administration of Angelica sinensis polysaccharide effectively improves fatty liver and glucose homeostasis in high-fat diet-fed mice. *Sci Rep* 2016;6(1):26229. Available at: http://doi.org/10.1038/srep26229
21. Heebøll S, Kreuzfeldt M, Hamilton-Dutoit S, et al. Placebo-controlled, randomised clinical trial: high-dose resveratrol treatment for non-alcoholic fatty liver disease. *Scand J Gastroenterol* 2016;51(4):456–64. Available at: http://doi.org/10.3109/00365521.2015.1107620
22. Reddyvari H, Govatati S, Matha SK, et al. Therapeutic effect of green tea extract on alcohol induced hepatic mitochondrial DNA damage in albino wistar rats. *J Adv Res* 2017;8(3):289–95. Available at: http://doi.org/10.1016/j.jare.2017.02.002
23. Zhu Y, Yang H, Deng J, Fan D. Ginsenoside Rg5 Improves Insulin Resistance and Mitochondrial Biogenesis of Liver via Regulation of the Sirt1/PGC-1α Signaling Pathway in db/db Mice. *J Agric Food Chem* 2021;69(30):8428–39. Available at: http://doi.org/10.1021/acs.jafc.1c02476
24. Zhang L, Han L, Ma R, et al. Sirt3 prevents maternal obesity-associated oxidative stress and meiotic defects in mouse oocytes. *Cell Cycle* 2015;14(18):2959–68. Available at: http://doi.org/10.1080/15384101.2015.1026517

Competing interests

The authors declare no conflicts of interest.

Abbreviations

NAFLD, Non-alcoholic fatty liver disease.

Citation

Wang S, Xing LW, Liao JB, Cui HT, Wen WB, Wang N. Repairing mitochondrial dysfunction: potential mechanisms of natural products in the treatment of NAFLD. *Gastroenterol Hepatol Res*. 2023;5(4):20. doi: 10.53388/ghr2023-03-084.

Executive editor: Na Liu.

Received: 30 December 2023, **Accepted:** 30 December 2023, **Available online:** 30 December 2023.